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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
LIN, JERRY	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/881,748	SHIOTA ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9,19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9,19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments, filed November 7, 2007, have been fully considered and they are not deemed to be persuasive. The following rejections are reiterated. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 6, 8, 9, 19, and 21-24 are under examination.

Claims 1-5, 7, 10-18, and 20 are cancelled.

Claim Rejections - 35 USC § 112, 1st Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8, 9, 19, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The instant claims have been amended to include the limitations of "differentiating stem cell", "a differentiating stem cell tissue", and "a differentiating stem cell nucleus". The applicants state in their remarks filed January 22, 2007, that although the phrase does not explicitly appear in the application, the phrase finds support in the

specification at page 13, lines 21-26 where it states "by determining whether the produced cells are stem cells or not by evaluating the degree of the stem cells." However, even within the context of the specification, it is unclear what is meant by degree of stem cells. For example, the specification mentions numerous types of cells that may be produced, page 13, lines 12-20, which are fully differentiated cells. Thus, one degree of a stem cell may be a fully differentiated cell, and the degree of a stem cell is not limited to a differentiating stem cell. Secondly, the specification does not appear to provide any examples of differentiating stem cells. Rather, the specification provides example of differentiated cells such as brain or intestine, or undifferentiated stem cells. Since the specification does not clearly support the limitation of "differentiating stem cells", the inclusion of this limitation is new matter.

Response to Arguments

3. Applicants have responded to this rejection by stating that that claims have been amended to clarify that "a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus" do not include fully differentiated cells. While this amendment clarifies the terms of "a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus", the specification as filed does not appear to recite any teaching of a differentiating stem cell, a differentiating stem cell tissue, or a differentiating stem cell nucleus.

Applicants also point to the teachings in the specification of differentiated cells and undifferentiated stem cells and suggest that one of skill in the art would have known

that undifferentiated stem cells may progress to differentiated cells. Applicants also provide literature for support of their position. Although the Examiner agrees with the Applicants that it was well known at the time of filing that undifferentiated stem cells could progress to differentiated stem cells, the *instant* specification must still teach the subject matter at the time of filing. In this instance, because the specification does not teach a differentiating stem cell, a differentiating stem cell tissue, or a differentiating stem cell nucleus, the specification does not teach finding the methylation patterns for these biological materials. In other words, support for these limitations must be found in the specification itself, and not derived from an outside source.

This rejection is maintained from the previous office action.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 19, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olek et al. (US 6,214,556 B1) in view of Labosky et al. (Development (1994) Volume 120, pages 3197-3204).

The instant claims are drawn to a method of identifying the differentiation state of a stem cell by comparing the methylation pattern of a stem cell to the methylation pattern of a cell of a known differentiation state.

Regarding claims 8 and 22 Olek et al. teaches a generic method of identifying cells types as well as cell states or stages though the use of methylation fingerprint patterns (column 14, lines 50-58; column 17, lines 30-40; column 2, lines 35-44; column 24-25). In his method he teaches obtaining a DNA methylation pattern for a test cell (columns 24-25) which comprises information the methylation of CpG at a plurality of gene regions (column 10, lines 6-16); obtaining a reference pattern for a particular cell type (columns 24-25); comparing the test cell DNA methylation pattern with the reference pattern (columns 24-25); and matching the test cell DNA methylation pattern with a reference pattern to determine the cell type (columns 24-25).

However, Olek et al. do not specifically teach using a reference pattern for differentiation states to determine the differentiation state of a stem cell. In other words, Olek et al. teach the generic version of the instant claims where a practitioner may use their method to determine any cell type or stage, but Olek et al. do not teach the instant

claims as the are specifically applied to differentiation states or where the differentiation state is undifferentiated as in claim 21.

Regarding claims 8, 19, 21 and 22, Labosky et al. provide the methylation patterns of embryonic germ cell lines (undifferentiated cells), embryonic stem cell lines, and compare the patterns of methylation of the embryonic germ cell lines and the embryonic stem cell lines (page 3200-3201)

One of ordinary skill in the art at the time the invention was made would have combined the methods of Olek et al. with the patterns discovered by Labosky et al. to create a method of identifying stem cells. Olek et al. teaches a generic method of identifying cell types though DNA methylation patterns. However in order to use Olek et al.'s method, one of ordinary skill in the art would have to find reference methylation patterns to which a sample methylation pattern can be compared. Labosky et al. provide such DNA methylation patterns. Thus one of ordinary skill in the art would be motivated to take the DNA methylation pattern Labosky et al. and incorporate it into Olek et al.'s method in order to identify unknown cell samples.

Response to Arguments

5. Applicants first question the reinstatement of this rejection after this rejection was withdrawn without providing the basis of reconsidering this rejection and the justification for reinstating this rejection. The Examiner apologizes for any inconvenience this has caused. However, upon reconsideration of the arguments provided by the applicants as well as the interview conducted on March 29, 2007 which clarified the subject matter

being claimed, the Examiner had deemed it necessary to reinstate this rejection. The Examiner has provided reasoning for reconsidering the arguments provided by the applicants below.

Applicants first argument to this rejection states that the references do not teach "obtaining a differentiation state-specific DNA methylation pattern one or more cell . . . . of a known differentiation state, wherein the one or more cell . . . is selected form a stem cell. . . ." as recited in claim 8 and that the references do not teach "obtaining a cell-. . . specific DNA methylation pattern for one or more known types of cell . . . wherein one or more known types of cell is selected form undifferentiated embryonic stell cell . . . . " as recited in claim 22. The Examiner disagrees. Labosky et al. provide the methylation patterns of embryonic germ cell lines (undifferentiated cells), embryonic stem cell lines, and compare the patterns of methylation of the embryonic germ cell lines and the embryonic stem cell lines (page 3200-3201). Applicants state that because Labosky teaches that the methylation pattern of the EG cells lines are characteristic of somatic cells and 5 different pluripotent ES cell lines and the methylation pattern of the other half of EG cells lines is different, Labosky et al. do not teach the limitations recited above. Although Labosky et al. have found differences and similarities in the methylation patterns of their stem cells, the methylation pattern are still the methylation patterns of stem cells as required by the claims. Thus Labosky et al. do anticipate the instant claims.

Applicants also state that Labosky et al. do not demonstrate that the methylation pattern is "differentiation state-specific" or "cell-, tissue, or nucleus-specific", because

half the EG cell lines share a certain methylation pattern while the other half has a different methylation pattern. However, Labosky et al. obtain methylation patterns of cells at a particular state. Although these methylation patterns may be similar to other cells, the methylation pattern is still specifically derived from a cell at a particular state. In other words, the methylation pattern that is specific to the cell at that state does not necessarily mean that the methylation pattern is unique to the cell at that state. Thus, Labosky et al. does teach the instant claim.

Because Labosky et al. teaches finding methylation patterns, and Olek teaches identifying cell types and cell states using methylation patterns, one of ordinary skill in the art at the time of the invention would have expected to be able to determine the cell state of a test cell by comparing the methylation patterns of the test cell and Labosky et al.'s methylation patterns.

This rejection is maintained from the previous office action.

6. Claims 6, 9, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olek et al. (US 6,214,556 B1) and Labosky et al. (Development (1994) Volume 120, pages 3197-3204) as applied to claims 8, 19, 21, and 22 above, and further in view of Ohgane et al. (Development Genetics Volume 22, pages 132-140).

The instant claims are drawn to a method of identifying the differentiation state of a stem cell by comparing the methylation pattern of a stem cell to the methylation

pattern of a cell of a known differentiation state where the methylation pattern includes at least 1,000 gene regions and the patterns are obtained by generating RLGS profiles.

Olek et al. and Labosky et al. are applied as above.

However, neither Olek et al. and Labosky et al. teach finding patterns in at least 1, 000 gene regions or using RLGS profiles.

Ohgane et al. teaches in the abstract and throughout, especially in Figure 1 and Tables 1-3, a comparison of methylation patterns at 2900 sites of polyploidy rat trophoblast giant cell DNA with that of diploid labyrinth zone and maternal kidney cells by use of the RLGS method. Four regions were sequenced to analyze the sequence of CpG island in the methylated regions.

It would have been obvious at the time of the invention to incorporate the methods taught by Ohgane et al. with Olek et al. and Labosky et al. to gain the benefit being able to generate methylation patterns of a large numbers of genes in order to make that pattern more specific for the state of a cell. Ohgane et al. teaches finding the methylation patterns of a large number of genes to ensure that the pattern is specific to the state of the cell. Thus one of ordinary skill in the art seeking to create specific methylation pattern for a cell would use Ohgane et al.'s strategy of using a large number of genes with the method of Olek et al. to identify an unknown cell sample.

Response to Arguments

7. Applicants have responded to this rejection by relying on their response to Olek et al. and Labosky et al. See above for the Examiner's response.

This rejection is maintained from the previous office action.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00-6:30, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JL/

/Marjorie A. Moran/
SPE, AU 1631
1/18/2008